EXCITOTOXINS

— DANGEROUS FOOD ADDITIVES —

Powerful excitotoxins like MSG and aspartame, found in processed foods, can bypass the blood-brain barrier, injuring the brain and exacerbating existing disease conditions.

Part 2 of 2

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EXCITOTOXINS AND THE BLOOD-BRAIN BARRIER

One of the MSG industry's chief arguments for the safety of its product is that glutamate in the blood cannot enter the brain because of the blood-brain barrier (BBB)—a system of specialised capillary structures designed to exclude toxic substances from entering the brain.

There are several criticisms of its defence. For example, it is known that the brain, even in the adult, has several areas—the circumventricular organs—that normally do not have a barrier system. These include the hypothalamus, the subfornical organ, organum vasculosum, area postrema, pineal gland and the subcommissural organ. Of these, the most important is the hypothalamus, since it is the controlling centre for all neuroendocrine regulation, sleep/wake cycles, emotional control, caloric intake regulation, and immune system and autonomic nervous system regulation.

As stated, glutamate is the most important neurotransmitter in the hypothalamus. Therefore, careful regulation of blood levels of glutamate is very important, since high blood concentrations of glutamate would be expected to increase hypothalamic levels as well. One of the earliest and most consistent findings with exposure to MSG is damage to an area of the hypothalamus known as the arcuate nucleus. This small hypothalamic nucleus controls a multitude of neuroendocrine functions and is also intimately connected to several other hypothalamic nuclei. It has also been demonstrated that high concentrations of blood glutamate and aspartate (from foods) can enter the so-called "protected brain" by seeping through the unprotected areas such as the hypothalamus or other circumventricular organs.

Another interesting observation is that chronic elevations of blood glutamate can even seep through the normal blood-brain barrier when these high concentrations are maintained over a long period of time.[44] This would be the situation seen when individuals consume, on a daily basis, foods high in the excitotoxins MSG, aspartame and L-cysteine. Most experiments cited by the defenders of MSG safety were conducted to test the efficiency of the BBB acutely. In nature, except in the case of metabolic dysfunction (such as with ALS, amyotrophic lateral sclerosis), glutamate and aspartate levels are not normally elevated on a continuous basis. Sustained elevations of these excitotoxins are peculiar to the modern diet (and in the ancient diets of Orientals, but not in as high a concentration).

An additional critical factor ignored by the defenders of excitotoxin food safety is the fact that many people in a large population have disorders known to alter the permeability of the blood-brain barrier. Conditions associated with barrier disruption include hypertension, diabetes, mini stroke, major stroke, head trauma, multiple sclerosis, brain infection, brain tumour, collagen-vascular disease (e.g., lupus), AIDS, Alzheimer's disease, as well as the effects of certain drugs, chemotherapy, radiation treatments to the nervous system and natural ageing. There may be many other conditions also associated with barrier disruption that are as yet not known. When the barrier is dysfunctional due to one of these conditions, brain levels of glutamate and aspartate reflect blood levels; that is, foods containing high concentrations of these excitotoxins will increase brain concentrations to toxic levels as well.

Take, for example, multiple sclerosis (MS). We know that when a person with MS has an exacerbation of symptoms, the blood-brain barrier near the lesions breaks down, leaving the surrounding brain vulnerable to excitotoxin entry from the blood, i.e., from the diet.[45] However, not only is the adjacent brain vulnerable, but the openings act as points of entry, eventually exposing the entire brain to potentially toxic levels of glutamate.

Several clinicians have remarked that their MS patients' conditions were made worse following exposure to dietary excitotoxins. I have seen this myself. It is logical to assume that the conditions of patients with other neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease and ALS, will be made worse on diets high in excitotoxins. Barrier disruption has been demonstrated in the case of Alzheimer's disease.[46]

Recently it was shown that not only can free radicals open the blood-brain barrier, but excitotoxins can as well.[47] In fact, glutamate receptors have been demonstrated on the barrier itself.[48] In a carefully designed experiment, researchers produced opening of the blood-brain barrier using injected iron as a free radical generator. When a powerful free radical scavenger (U-74006F) was used in this model, opening of the barrier was significantly blocked, but the glutamate blocker (MK-801) acted even more effectively to protect the barrier. The authors of this study concluded that glutamate appears to be an important regulator of brain capillary transport and stability, and that overstimulation of NMDA (glutamate) receptors on the blood-brain barrier appears to play an important role in breakdown of the barrier system. What this also means is that high levels of dietary glutamate or aspartate may very well disrupt the normal blood-brain barrier, thus allowing more glutamate to enter the brain, creating a vicious cycle.

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CELLULAR ENERGY

Excitotoxin damage is heavily dependent on the energy state of the cell.[49] Cells with a normal energy generation system are very resistant to such toxicity. When cells are energy deficient, no matter the cause—hypoxia, starvation, metabolic poisons, hypoglycaemia—they become infinitely more susceptible to excitotoxic injury or death. Even normal concentrations of glutamate are toxic to energy-deficient cells.

It is known that in many of the neurodegenerative disorders, neuron energy deficiency often precedes the clinical onset of the disease by years, if not decades.[50] This was demonstrated in the case of Huntington's disease and Alzheimer's disease, using the PET scanner which measures brain metabolism. In the case of Parkinson's disease, several groups demonstrated that one of the early deficits of the disorder is an impaired energy production by the complex I group of enzymes within the mitochondria of the substantia nigra.[51, 52] Interestingly, it is known that the complex I system is very sensitive to free radical damage.

Recently it was shown that when striatal neurons are exposed to micro-injected excitotoxins, there is a dramatic and rapid fall in energy production by these neurons. In this model, co-enzyme Q10 was shown to restore energy production but not to prevent cellular death. But, when combined with niacinamide, both cellular energy production and neuron protection was seen.[53] For those with neurodegenerative disorders, I recommend a combination of CoQ10, acetyl-L carnitine, niacinamide, riboflavin, methylcobalamin and thiamine.

One of the newer revelations of modern molecular biology is the discovery of mitochondrial diseases, of which cellular energy deficiency is a hallmark. In many of these disorders, significant clinical improvement is seen following a similar regimen of vitamins combined with CoQ10 and L-carnitine.[54] Acetyl L-carnitine enters the brain in higher concentrations and also increases brain acetylcholine, necessary for normal memory function. While these particular substances are found to boost brain energy function significantly, they are not alone in this important property. Phosphotidyl serine, ginkgo biloba, vitamin B12, folate, magnesium, vitamin K and several other substances are also shown to be important.

While mitochondrial dysfunction is important in explaining why some people are more vulnerable to excitotoxin damage than others, it does not explain injury in those with normal cellular metabolism. There are several conditions under which energy metabolism is impaired. We know, for example, that approximately one-third of Americans suffer from reactive hypoglycaemia; that is, they respond to a meal composed of either simple sugars or carbohydrates (that are quickly broken down into simple sugars, i.e., a high glycaemic index) by secreting excessive amounts of insulin, which causes a dramatic lowering of the blood sugar. When the blood sugar level falls, the body responds by releasing a burst of epinephrine from the adrenal glands in an effort to raise the blood sugar. This release is felt as nervousness, palpitations of the heart, tremulousness and profuse sweating. Occasionally we can have a slower fall in the blood sugar that will not produce a reactive release of epinephrine, thereby producing few symptoms. This can be more dangerous, since we are unaware that our glucose reserve is falling until we develop obvious neurological symptoms, such as difficulty thinking and a sensation of lightheadedness.

The brain is one of the most glucose-dependent organs known, since it has a limited ability to metabolise other substrates such as fats. There is some evidence that several of the neurodegenerative diseases are related to either excessive insulin release, as with Alzheimer's disease, or impaired glucose utilisation, as we have seen in the case of Parkinson's disease and Huntington's disease.[55]

It is my firm belief, based on clinical experience and physiological principles, that many of these diseases occur primarily in the face of either reactive hypoglycaemia or "brain hypoglycaemia", a condition where the blood sugar is normal and the brain is hypoglycaemic in isolation. In at least two well-conducted studies, it was found that pure Alzheimer's dementia was rare in those with normal blood sugar profiles, and that in most cases Alzheimer's patients had low blood sugar and high CSF (cerebrospinal fluid) insulin levels.[56, 57] In my own limited experience with Parkinson's and ALS patients, I found a disproportionately high number suffering from reactive hypoglycaemia.

I find it interesting that several ALS patients observed an association between their symptoms and gluten: when they adhered to a gluten-free diet, their clinical symptoms improved. It may be that by avoiding gluten-containing products, such as bread, crackers, cereal, pasta, etc., they are also avoiding products that are high on the glycaemic index, i.e., that produce reactive hypoglycaemia. Also, all of these food items are high in free iron. Clinically, hypoglycaemia worsens the symptoms of most neurological disorders. We know that severe hypoglycaemia can in fact mimic ALS both clinically and pathologically.[58] It is also known that many of the symptoms of Alzheimer's disease resemble hypoglycaemia, as if the brain is hypoglycaemic in isolation.

In studies of animals exposed to repeated, mild episodes of hypoxia (lack of brain oxygenation), it was found that such accumulated injuries can trigger biochemical changes that resemble those seen in Alzheimer's patients.[59] One of the effects of hypoxia is a massive release of glutamate into the space around the neuron, which results in the rapid death of these sensitised cells. As we age, the blood supply to the brain is frequently impaired, either because of atherosclerosis or repeated syncopal episodes, leading to short periods of hypoxia. Hypoglycaemia produces lesions very similar to hypoxia and via the same glutamate excitotoxic mechanism. In fact, recent studies of diabetics suffering from repeated episodes of hypoglycaemia associated with insulin overmedication have demonstrated brain atrophy and dementia.[60]

Another cause of isolated cerebral hypoglycaemia is the impaired transport of glucose into the brain across the blood-brain barrier. It is known that glucose enters the brain by way of a glucose transporter, and that in several conditions, including arteriosclerosis, Alzheimer's disease and ageing, this transporter is impaired.[61, 62] This is especially important in the diabetic, since prolonged elevation of the blood sugar produces a down-regulation of the glucose transporter and a concomitant brain hypoglycaemia that is exacerbated by repeated spells of peripheral hypoglycaemia common to type-I diabetics.

With ageing, we see several of these energy deficiency syndromes, such as mitochondrial injury, impaired cerebral blood flow, enzyme dysfunction and impaired glucose transportation, develop simultaneously. This greatly magnifies excitotoxicity, leading to accelerated free radical injury, a progressively rapid loss of cerebral function and profound changes in cellular energy production.[63] It is suspected that at least in some of the neurodegenerative diseases (in particular, Alzheimer's dementia and Parkinson's disease), this series of events plays a major pathogenic role.[64] Chronic free radical accumulation also results in an impaired functional reserve of antioxidant vitamins/minerals, antioxidant enzymes (superoxide dismutase or SOD, catalase and glutathione peroxidase) and thiol compounds necessary for neural protection. Chronic unrelieved stress, chronic infection, free radical generating metals and toxins, and impaired DNA repair enzymes all add to this damage.

It is estimated that oxidative free radical injuries to DNA number about 10,000 a day in humans.[65] Under conditions of cellular stress, these may reach several hundred thousand. Normally, these injuries are repaired by special DNA repair enzymes. It is known that these repair enzymes decrease in number or become less efficient as we age.[66] Also, some individuals are born with deficient repair enzymes, as in the case of xeroderma pigmentosum, for example. Recent studies of Alzheimer's patients also demonstrate a significant deficiency in DNA repair enzymes and high levels of lipid peroxidation products in the affected parts of the brain.[67, 68] It is important to realise that the hippocampus, most severely damaged in Alzheimer's dementia, is one of the areas of the brain most vulnerable to low glucose supply as well as low oxygen supply. That also makes it very susceptible to glutamate/free-radical toxicity.

Another interesting finding is that when cells are exposed to glutamate, they develop certain inclusions (cellular debris) which not only resemble the characteristic neurofibrillary tangles of Alzheimer's dementia but are immunologically identical as well.[69] Similarly, when experimental animals are exposed to the chemical MPTP they develop Parkinson's disorder; in fact, the older animals develop the same inclusions (Lewy bodies) as seen in human Parkinson's.[70] There is growing evidence that protracted glutamate toxicity leads to a condition of receptor loss characteristic of neurodegeneration.[71] This receptor loss produces a state of disinhibition which magnifies excitotoxicity during the later stage of the neurodegenerative process.

SPECIAL FUNCTIONS OF ASCORBIC ACID

The brain contains one of the highest concentrations of ascorbic acid in the body. Most are aware of ascorbic acid's function in connective tissue synthesis and as a free radical scavenger, but it has other functions that make it rather unique.

In man, we know that certain areas of the brain have very high concentrations of ascorbic acid, such as the nucleus accumbens and hippocampus. The lowest levels are seen in the substantia nigra.[72] These levels seem to fluctuate with the electrical activity of the brain. Amphetamine acts to increase ascorbic acid concentration in the corpus striatum (basal ganglion area) and decrease it in the hippocampus, the memory imprint area of the brain. Ascorbic acid is known to play a vital role in dopamine production as well.

There is now substantial evidence that ascorbic acid modulates the electrophysiological as well as behavioural functioning of the brain. This could mean that ascorbic acid holds great potential in treating disease related to excitotoxic damage.

One of the more interesting links is between the secretion of the glutamate neurotransmitter by the brain and the release of ascorbic acid into the extracellular space.[73] This release of ascorbate can also be induced by systemic administration of glutamate or aspartate, as would be seen in diets high in these excitotoxins. The other neurotransmitters do not have a similar effect on ascorbic acid release. This effect appears to be an exchange mechanism; that is, the ascorbic acid and glutamate exchange places. Theoretically, high concentration of ascorbic acid in the diet could inhibit glutamate release, lessening the risk of excitotoxic damage. Of equal importance is the free radical neutralising effect of ascorbic acid.

There is now substantial evidence that ascorbic acid modulates the electrophysiological as well as behavioural functioning of the brain.[74] It also attenuates the behavioural response of rats exposed to amphetamine, which is known to act through an excitatory mechanism.[75] In part, this is due to the observed binding of ascorbic acid to the glutamate receptor. This could mean that ascorbic acid holds great potential in treating disease related to excitotoxic damage. Thus far, there are no studies relating ascorbate metabolism in neurodegenerative diseases. There is at least one report of ascorbic acid deficiency in guineas pigs producing histopathological changes similar to ALS.[76]

It is known that as we age there is a decline in brain levels of ascorbate. When accompanied by a similar decrease in glutathione peroxidase, we see an accumulation of H_3O_2 and, hence, elevated levels of free radicals and lipid peroxidation. In one study it was found that, with age, not only does the extracellular concentration of ascorbic acid decrease but the capacity of the brain ascorbic acid system to respond to oxidative stress is impaired as well.[77]

In terms of its antioxidant activity, vitamins C and E interact in

such a way as to restore each other's active antioxidant state. Vitamin C scavenges oxygen radicals in the aqueous phase and vitamin E in the lipid, chain-breaking phase. The addition of vitamin C suppresses the oxidative consumption of vitamin E almost totally, probably because in the living organism the vitamin C in the aqueous phase is adjacent to the lipid membrane layer containing the vitamin E.

When combined, the vitamin C is consumed faster during oxidative stress than is vitamin E. Once the vitamin C is totally consumed, vitamin E begins to be depleted at an accelerated rate. N-acetyl-L-cysteine and glutathione can reduce vitamin E consumption as well, but less effectively than vitamin C.

The real danger is when vitamin C is combined with iron. This is because the free iron oxidises the ascorbate to produce the free radical, dehydroxyascorbate. Alpha-lipoic acid acts powerfully to keep the ascorbate and tocopherol in the reduced state (antioxidant state). As we age, we produce less of the transferrin transport protein that normally binds free iron. As a result, older individuals have higher levels of free iron within their tissues, including brain, and are therefore at greater risk of widespread free radical injury.

Likewise, excess glutamate can cause neural pathways to produce improper connections—a process I call "miswiring of the brain".

IMPLICATIONS FOR NEURODEVELOPMENT

Recent studies have shown that glutamate plays a vital role in the development of the nervous system, especially as regards neuronal survival, growth and differentiation, development of circuits and cytoarchitecture.[78]

For example, it is known that deficiencies of glutamate in the brain during neurogenesis can result in maldevelopment of the visual cortices and may play a role in the development of schizophrenia.[79] Likewise, excess glutamate can cause neural pathways to produce improper connections—a process I call "miswiring of the brain". Excess glutamate during embryogenesis has been shown to reduce dendritic length and suppress axonal outgrowth in hippocampal neurons. It is interesting to note that glutamate can produce classic toxicity in the immature brain, even before the glutamate receptors develop. High glutamate levels can also affect astroglial proliferation as well as neuronal differentiation. It appears to act via the phosphoinositide protein kinase C pathway.

It has been shown that during brain development there is an overgrowth of neuronal connections and cellularity, and that at this stage there is a peak in levels of brain glutamate, whose function it is to remove excess connections and neuronal overexpression. This has been referred to as "pruning". Importantly, glutamate excess during synaptogenesis and pathway development has been shown to cause abnormal connections in the hypothalamus that can lead to later endocrinopathies.[80]

In general, toxicological injury in the developing foetus carries the greatest risk during the first two trimesters. But this is not so for the brain, which undergoes a spurt of growth that begins during the third trimester and continues at least two years after birth. Dendritic growth is maximal in the late foetal period to one year of age, but may continue at a slower pace for several more years. Neurotransmitter development also begins during the late foetal period, but continues for as long as four years after birth. This means that alterations in dietary glutamate and aspartate are especially dangerous to the foetus during pregnancy and for several years after birth.

The developing brain's susceptibility to excitotoxicity varies, since each brain region has a distinct developmental profile. The type of excitotoxin also appears to matter. For example, kianate is non-toxic to the immature brain but extremely toxic to the mature brain. The glutamate agonist NMDA is especially toxic up to postnatal day seven, while quisqualate and AMPA have peak toxicity from postnatal day seven through fourteen. L-cysteine is a powerful excitotoxin on the immature brain.

Myelination can also be affected by neurotoxins. In general,

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excitotoxic substances affect dendrites and neurons more than axons, but axon demyelination has been demonstrated. During the myelination process, each fibre tract has its own spatiotemporal pattern of development, accompanied by significant biochemical changes especially in lipid metabolism.

More recent studies have shown an even more complicated pattern of CNS myelination than previously thought. This is of importance, especially as regards the widespread use of aspartame because of this triple toxin's effects on neuronal proteins and DNA. Of special concern is aspartame's methanol component and its breakdown product, formaldehyde.[81] Also, it is known that the aspartate moiety undergoes spontaneous racemisation in hot liquids to form D-aspartate, which has been associated with tau proteins in Alzheimer's disease.[82, 83]

As you can see, the development of the brain is a very complex process that occurs in a spatial and temporal sequence that is carefully controlled by biochemical, structural as well as neurophysiological events. Even subtle changes in these parameters can produce ultimate changes in brain function that may vary from subtle alteration in behaviour and learning to autism, attention deficit disorder and violence dyscontrol.[84, 85, 86]

Experiments in which infant animals were exposed to MSG have demonstrated significant neurobehavioural deficits.[87, 88] Other studies have shown that when pregnant female animals were fed MSG, their offspring demonstrated normal, simple learning but showed significant deficits in complex learning, accompanied by profound reductions in several forebrain neurotransmitters.[89, 90] In humans, this would mean that during infancy and early adolescence, learning would appear normal; but with entry into a more advanced education level, learning would be significantly impaired. In several ways, this animal model resembles ADD and ADHD in humans. Kubo and co-workers found that neonatal glutamate could severely injure hippocampal CA1 neurons and dendrites and, as a result, impair discriminative learning in rats.[91]

It is also important to note that neonatal exposure to MSG has been shown to cause significant alterations in neuroendocrine function that can be prolonged.[92, 93] By acting on the hypothalamus and its connections to the remainder of the limbic connections, excitotoxins can profoundly affect behaviour.

CONCLUSION: PREVENTING EXCITOTOXIC INJURY

In this brief discussion of a most complicated and evolving subject, I have had to omit several important pieces of the puzzle. For example, I have said little about the functional components of the receptor systems, the glutamate transporter and its relation to ALS and Alzheimer's dementia, receptor decay with ageing and disease, membrane effects of lipid peroxidation products, membrane fluidity, effects of chronic inflammation on the glutamate/free-radical cycle, stress hormones and excitotoxicity, the role of insulin excess on the eicosanoid system, and the detailed physiology of the glutamatergic system.

I have also only briefly alluded to the toxicity of aspartame and omitted its strong connection to brain tumour induction.

I have also only briefly alluded to the toxicity of aspartame and omitted its strong connection to brain tumour induction.

I have tried to show the reader that there is a strong connection between dietary and endogenous excitotoxin excess and neurological dysfunction and disease. Many of the arguments by the food processing industry have been shown to be false. For example, that dietary glutamate does not enter the brain because of exclusion by the blood-brain barrier has been shown to be wrong, since glutamate can enter by way of the unprotected areas of the brain, such as the circumventricular organs. Also, as we have seen, chronic elevations of blood glutamate can breach the intact blood-brain barrier. In addition, there are numerous conditions under which the barrier is made incompetent.

As our knowledge of the pathophysiology and biochemistry of the neurodegenerative diseases increases, the connection to excitotoxicity has become stronger.[94] This is especially so with the interrelationship between excitotoxicity and free radical

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generation and declining energy production with ageing. Several factors of ageing have been shown to magnify this process. For example, as the brain ages, its iron content increases, making it more susceptible to free radical generation. Also, ageing changes in the blood-brain barrier, microvascular changes leading to impaired blood flow, free radical mitochondrial injury to energy-generating enzymes, DNA adduct formation, alterations in glucose and glutamate transporters, and free radical and lipid peroxidation induced alterations in the neuronal membranes all act to make the ageing brain increasingly susceptible to excitotoxic injury.

Over a lifetime of free radical injury due to chronic stress, infections, trauma, impaired blood flow, hypoglycaemia, hypoxia and poor antioxidant defences secondary to poor nutritional intake, the nervous system is significantly weakened and made more susceptible to further excitotoxic injury. We know that a loss of neuronal energy generation is one of the early changes seen with the neurodegenerative diseases. This occurs long before clinical disease develops. But, even earlier is a loss of neuronal glutathione functional levels.

I included the material about the special function of ascorbic acid because few are aware of the importance of adequate ascorbate levels for CNS function and neural protection against excitotoxicity. As we have seen, it plays a vital role in neurobehavioural regulation and the dopaminergic system as well, which may link ascorbate supplementation to improvements in schizophrenia.

Our knowledge of this process opens up new avenues for treatment as well as prevention of excitotoxic injury to the nervous system. For example, there are many nutritional ways to improve CNS antioxidant defences and boost neuronal energy generation, as well as improve membrane fluidity and receptor integrity. By using selective glutamate-blocking drugs or nutrients, one may be able to alter some of the more devastating effects of Parkinson's disease. For example, there is evidence that dopamine deficiency causes a disinhibition (overactivity) of the subthalamic nucleus and that this may result in excitotoxic injury to the substantia nigra.[95] By blocking the glutamatergic neurons in this nucleus, one may be able to reduce this damage. There is also evidence that several nutrients can significantly reduce excitotoxicity. For example, combinations of coenzyme Q10 and niacinamide have been shown to protect against striatal excitotoxic lesions. Methylcobolamin, phosphotidylserine, pycnogenol and acetyl-L-carnitine all protect against excitotoxicity as well.

Other hypothalamic syndromes associated with early excitotoxic lesions include immune alterations and violence dyscontrol.

Over 100 million Americans now consume aspartame products, and a greater number consume products containing one or more excitotoxins.

Of particular concern are the toxic effects of these excitotoxic compounds on the developing brain. It is well recognised that the immature brain is four times more sensitive to the toxic effects of the excitatory amino acids as is the mature brain.

This means that excitotoxic injury is of special concern from the foetal stage to adolescence. There is evidence that the placenta concentrates several of these toxic amino acids on the foetal side of the placenta. Consumption of aspartame- and MSG-containing products by pregnant women during this critical period of brain formation is of special concern and should be discouraged.

Many of the effects, such as endocrine dysfunction and complex learning difficulties, are subtle and may not appear until the child is older. Other hypothalamic syndromes associated with early excitotoxic lesions include immune alterations and violence dyscontrol.

Over 100 million Americans now consume aspartame products, and a greater number consume products containing one or more excitotoxins.

There is sufficient medical literature documenting serious injury by these additives in the concentrations presently in our food supply to justify warning the public of these dangers. The case against aspartame is especially strong. ∞

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